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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,605	07/27/2001	Marcel Koken	US471	1616

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,605	KOKEN ET AL.	
	Examiner	Art Unit	
	Karen A. Canella '	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-19,21,24 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-19,21,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/26/01+7/27/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 20, 22 and 23 have been canceled. Claims 12-19, 21, 24 and 25 have been amended and are under consideration.

2. Sections of Title 35 U.S. Code not found in this action can be found in a previous action.

3. The rejection of claims 24 and 25 under 35 U.S.C. 102(e) as being anticipated by Kaltoft et al (US 2002/0001841, priority to July 2, 1998, 60/091,684) is maintained for reasons of record.

Claims 24 and 25 are drawn in part to a method of inducing the death of undesirable cells or stimulation of an immune response comprising administering to a patient a caspase inhibitor and/ or a caspase substrate.

Kaltoft et al disclose a method of treating diseases, such as those of neoplastic origin [0080], comprising administration of specific disease-associated T-cells to a patient in need thereof [0150]. Kaltoft et al teach that the caspase inhibitor, z-VAD may be given during the administration to prevent AICD of the infused lymphocytes [0150]. The instant claims are drawn to a method comprising the administration of a caspase inhibitor and do not exclude methods comprising other active agents, such as disease associated T-cells.

4. Applicants arguments regarding the lack of induction of apoptosis by the synergistic combination of zVAD and interferons is moot regarding claims 24 and 25 because the instant claims are drawn only to the administration of a caspase inhibitor and do not require the administration of an interferon, and no requirement is made for the induction of a specific type of cell death..

5. The rejection of claims 12-14, 16-19 and 21 under 35 U.S.C. 103(a) as being unpatentable over He et al (Anticancer Research, 1997, Vol. 17, No. 5C, page 3927, abstract #6) in view of Muller et al (EMBO, Jan 2, 1998, vol. 17, pp. 61-70) and Chelbi-Alix et al (NATO ASI Series H: Cell Biology (1996, Vol. 99 (Tumor Biology),.pp. 17-27) is maintained in part.

He et al teach the administration of retinoic acid, IFN, arsenic trioxide , melarsoprol, or combinations thereof in transgenic models of APL. He et al do not specifically teach the combination of IFN and arsenic trioxide, or IFN and melarsoprol.

Muller et al teach that the post-translational modification of PML with SUMO-1 modulates the intracellular location of PML. Muller et al teach that arsenic trioxide increases the amount of PML-1-SUMO-1 conjugates that accumulate in the nuclear bodies. Muller et al teach that when ATL cells are exposed to arsenic trioxide PML-RARalpha is rapidly degraded but PML is not degraded (page 68, first column, lines 28-30). Muller et al teach that the kinetics of restoration of nuclear bodies is a direct consequence of PML-RARalpha destruction. Muller et al do not teach the molecular consequences of the administration of arsenic trioxide and interferon.

Chelbi-Alix et al teach that the PML/RARalpha fusion protein has been identified in acute promyleocytic leukemia, wherein the chimeric protein s a product of a t(15;17) translocation rendering RARalpha under control of the PML promoter. Chelbi-Alix et al teach that the PML/RARalpha fusion protein contains the functional domains of both PML and RARalpha and is the likely molecular basis of APL leukaemogenesis probably through alteration of PML and/or RARalpha functions (page 19, lines 1-13). Chelbi-Alix et al teach that in APL the PML/RARalpha fusion protein displaces the PML protein into microspeckeles rather than the normal location of nuclear bodies. Chelbi-Alix et al teach that the microspeckles are smaller and much more numerous than the speckled nuclear bodies (page 19, lines 15-25). Chelbi-Alix et al teach that IFNalpha treatment of NB4 cells increases the micropunctuate pattern of PML and PML/RARalpha without altering their abnormal microspeckled location (without restoring the nuclear bodies) (page 21, lines 9-11). Chelbi-Alix et al teach that because IFNalpha increases PML/RARalpha in addition to PML, treatment with IFNalpha may enhance binding to RXR resulting in a further impairment of retinoic acid receptor function, which would act to increase the differentiation block toward nuclear receptors (page 21, line 12 to page 22, line 2). Chelbi-Alix et al teach that the demonstration that IFNalpha induces PML/RARalpha in APL cells is consistent with observations that the use of interferon in the treatment of APL can accelerate a patients leukemia (page 22, lines 7-10). Chelbi-Alix et al teach that over expression of PML retards cell growth and PML sharply reduces the transforming effects of cooperating

oncogenes and suppresses transformation by activated neu oncogene (page 23, line 4 to page 24, line 2). Chelbi-Alix et al conclude that IFN-induced PML protein has anti-oncogenic effects (page 24, lines 2-3).

It would have been prima facie obvious to one of skill in the art to combine arsenic trioxide with interferon for the treatment of leukemias associated with the fusion protein PML/RARalpha, or for the in vitro inhibition of said leukemia cells. One of skill in the art would be motivated to do so by the teachings of Muller et al on the selective degradation of the PML/RARalpha fusion protein after exposure of HTLV-1 associated ATL cells to arsenic trioxide; and the teachings of Chelbi-Alix on the anti-oncogenic effects of the PML protein and the induction of both the PML and PML/RARalpha proteins by exposure of APL cells to interferon alpha. One of skill in the art would have concluded that while the effects of arsenic trioxide on the selective degradation of the PML/RARalpha fusion protein are desirable, the addition of interferon would be t least additive in effect because it would be expected that the induction of PML would exert an anti-oncogenic effect and the concomitant induction of PML/RARalpha would be neutralized by arsenic trioxide degradation. Thus, one of skill in the art would expect that leukaemogenesis would be reversed by the decrease or elimination of PML/RARalpha and the increase in PML.

6. Applicant has amended claims 12 and 19 to require that the death of the undesirable cells is not due to apoptosis. The combination of cited references above supports the examiners contention that one of skill in the art would be motivated to combine teachings of Muller et al regarding the selective degradation of PML-RARalpha by arsenic compounds and the teachings of Chelbi-Alix et al regarding the desirability of maintaining a level of PML protein which was not PML-RARalpha and the ability of interferons to induce levels of PML and PML-RARalpha. The mode of cell death induced as a consequence of the combined administration of interferons and an arsenic compound would be inherent in the exposure of the leukemic cells to both of arsenic and interferon. It is further noted that claim 21 does not require a specific mode of cell death, therefore applicants arguments regarding a non-apoptotic cell death are moot with regard to claim 21.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 12-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing cell death comprising the administration of arsenic or arsenic derivative or zVAD or DEVD which promotes the targeting of PML to the nuclear bodies and the administration of a agent which induces the over expression of the PML protein wherein the death of undesirable cells is not due to apoptosis, does not reasonably provide enablement for a method of stimulating an immune response comprising the administration of a substance which promotes the targeting of PML to the nuclear bodies and the administration of a agent which induces the over expression of the PML protein wherein the death of undesirable cells is not due to apoptosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

(A) As drawn to the stimulation of an immune response

The post-filing date art (Quignon et al, Nature Genetics, 1998, Vol. 20, pp. 259-265, reference of the IDS filed July 26, 2001) teaches that arsenic and zVAD enhance PML and IFN-induced apoptosis. The specification specifically teaches that the exposure of cells over expressing the PML protein to arsenic in combination with interferons, or zVAD or DEVD (page 17, lines 18-19) causes a type of cell death which does not exhibit characteristics typical of apoptosis , such as condensation of chromatin and nuclear fragmentation (page 7, lines 10-14 and 20-21). It is noted that the specification is mute about the integrity of the plasma membrane, a feature which is a defining characteristic of necrosis Quignon et al teach that PML-mediated cell death is a central and unexpected cell death pathway which is independent of caspases (page 264, first column, lines 12-15 and lines 32-37, under the heading "A novel and central cell death pathway?"). Quignon et al teach the characteristics of this death pathway to include cytoplasmic shrinkage, appearance of sub-G1 DNA, membrane phosphatidly serine externalization and loss of mitochondrial transmembrane potential (page 260 first column, lines 10-17). Quignon et al

specifically note that the cells retained the ability to exclude trypan blue (page 260, first column, lines 17-18). Quignon et al conclude that although DNA cleavage was occurring as evidence by the presence of sub-G1 DNA, internucleosomal DNA laddering was not observed (page 260, first column, lines 21-25). These findings are consistent with those reported in the specification. Perry et al (Biotechniques, 1997, Vol. 22, pp. 1102-1106) teach that although membrane permeability is characteristic of necrosis and DNA fragmentation is characteristic of apoptosis, the oligonucleosomal degradation of DNA is not a prerequisite for apoptosis (page 1102, second column, lines 46-51) and that some cells exhibit morphological features of apoptosis within any DNA fragmentation (page 1103, first column, lines 1-4). It can be reasonably concluded that the PML-induced cell death pathway, although not a "typical" apoptotic death pathway, is not a necrotic death pathway because membrane integrity is preserved as is evident by the exclusion of trypan blue dye. Lutz et al (Trends in Immunology, 2002, Vol. 23, pp. 445-449) teach that only fully mature dendritic cells are able to induce an immune response, and that semi-mature or immature dendritic cells , when confronted with antigen induce tolerance (abstract, lines 4-7). Sauter et al (Journal of Experimental Medicine, 2000, Vol. 191, pp. 423-433) teach that necrotic tumor cells, in contrast to apoptotic cells induce maturation of dendritic cells (page 430, first column, lines 3-9). Neither the specification, nor any art of record supports necrosis as a cell death pathway mediated by the PML protein. Thus, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the claimed methods to the extent that they read on the stimulation of an immune response.

(B) As drawn to a method of inducing cell death comprising administering a substance which is not an arsenic derivative, z-VAD-Fmk or DEVD-Fmk.

The instant claims are broadly drawn to the induction of a PML cell death pathway by the synergistic action of an agent which is PML or an agent which induces the over expression of PML. Quignon et al (ibid) teach that z-VAD accelerated interferon induced cell death, but that the caspase inhibitor, BD, had no effect (ibid, page 261, second column, lines 17-20 under the heading "Arsenic and zVAD enhanced PML- and IFN-induced apoptosis"). The specification reports results for the caspase inhibitor DEVD (page 17, lines 18-19). Thus, it appears that there is no nexus between the synergism observed between interferon and zVAD or DEVD and the broadly claimed methods relying on a large genus of caspase inhibitors and caspase substrates.

One of skill in the art would be subject to undue experimentation in order to practice the claimed method with "caspase inhibitors" and "caspase substrates" because it would be required to screen each caspase inhibitor or caspase substrate to identify those which worked, and the specification does not provide any guidance for the identification of there is no reasonable expectation of success that the genus can be extended beyond that of zVAD-Fmk or DEVD-Fmk in light of the fact that the caspase inhibitor BD failed to function as claimed.

9. Claims 12, 13, 16-19 and 21 are rejected under 35 U.S.C. 102(e) as being anticipated by Lu (U.S. 6,733,792).

Lu dislcoses a method for the treatment of leukemias which include acute promyelocytic leukemia comprising the administration of arsenic sulfide and interferons, wherein the arsenic sulfide can be adminsitered before during or after the interferons (column 10, line 60, column 11, line 18-20 and column 12, lines 3-14) . The induction of PML overexpression as a result of the adminsitered interferon would result from the treatment with arsenic trioxide and interferon. Lu dislcoses "interferons" as a general class whihc includes all of interferons alpha, beta and gamma.

10. All other rejections and objections as set forth in the previous Office action are withdrawn in light of applicants arguements and submission of the translated priority document.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
5/9/2005

KAREN A. CANELLA PH.D
PRIMARY EXAMINER